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An abundance of seafood consumption studies presents new opportunities to evaluate effects on neurocognitive development

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A B S T R A C T

The relationship between seafood eaten during pregnancy and neurocognition in offspring has been the subject of considerable scientific study for over 25 years. Evaluation of this question led two scientific advisory committees to the Dietary Guidelines for Americans (DGAC), the Food and Agriculture Organization of the United Nations with the World Health Organization (FAO/WHO), Health Canada, the European Food Safety Authority (EFSA), and the U.S. Food and Drug Administration (FDA) to conclude through 2014 that seafood consumed by pregnant women is likely to benefit the neurocognitive development of their children. The evidence they reviewed included between four and ten studies of seafood consumption during pregnancy that reported beneficial associations. In contrast there are now 29 seafood consumption studies available describing over 100,000 mothers-child pairs and 15 studies describing over 25,000 children who ate seafood. A systematic review of these studies using Nutrition Evaluation Systematic Review methodology is warranted to determine whether recent research corroborates, builds on, or significantly alters the previous conclusions. Studies that evaluate the integrated effects of seafood as a complete food more directly and completely evaluate impacts on neurocognition as compared to studies that evaluate individual nutritients or toxicological constituents in isolation. Here we address how the findings could add to our understanding of whether seafood consumed during pregnancy and early childhood affects neurocognition, including whether such effects are clinically meaningful, lasting, related to amounts consumed, and affected by any neurotoxicants that may be present, particularly mercury, which is present at varying levels in essentially all seafood. We provide the history, context and rationale for reexamining these questions in light of currently available data.

AAP,	American Academy of Pediatrics;
AHRQ,	Agency for Healthcare Research and Quality;
DGA,	Dietary Guidelines for Americans;
DGAC,	Dietary Guidelines Advisory Committee;
DHA,	docosahexaenoic acid;
EFSA,	European Food Safety Authority, FAO/WHO, Food and Agriculture Organization/World Health Organization;
FDA,	U.S Food and Drug Administration;
IOM,	Institute of Medicine of the National Academy of Sciences;
NESR,	Nutrition Evaluation Systematic Review;
RCTs,	randomized controlled trials.

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1. Current developments present a major opportunity

The 2020–2025 Dietary Guidelines for Americans[1] (DGA) will address the following two questions:

> "What is the relationship between seafood consumption during pregnancy and lactation and the neurocognitive development of the infant? What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and neurocognitive development?" [1]

The answers to these questions could have significant public health impacts. The questions are also appropriate because there is considerably more published research available for evaluation since a systematic review of the evidence was conducted for the 2010–2015 DGA [2] and subsequent reviews were conducted by other entities through 2014 [3–7]. The inclusion of term "seafood"[2] in these questions is significant because the 2020–2025 DGA will likely make recommendations for consuming seafood as a whole food in addition to any recommendations it may make about individual nutrients, e.g., fatty acids within seafood.

Evaluating seafood consumption is inherently a "net effects" evaluation that implicitly "reflect[s] the sum of benefits and risks from all of the constituents in the fish" [3, p. 8]. As a practical matter, net effects are differences between scores on tests of neurocognition when seafood has been consumed (either by pregnant women or by children) and scores on the same tests when little or no seafood has been consumed. The differences, such as there may be, are measurable in study populations even if the contributions from individual constituents in seafood are not measured or even clearly understood. The sum of risks and benefits, i.e., the net effects from eating seafood under a plausible range of circumstances, essentially answers the two questions about seafood to be addressed by the 2020–2025 DGA.

To evaluate these questions, we have conducted two systematic reviews utilizing methodologies detailed by the Dietary Guidelines for Americans Scientific Advisory Committee 2020–2025, USDA's Nutrition Evidence Systematic Review (NESR) team (https://nesr.usda.gov). This process is designed to be rigorous and transparent, such that it can be replicated by qualified professionals [https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews]. These reviews are reported in our accompanying article entitled: "Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: two systematic reviews." These systematic searches and reviews of scientific databases identified 29 studies that examined relationships between seafood consumption during pregnancy and neurocognitive outcomes in over 100,000 children and 15 studies that examined the relationship between seafood consumed by over 25,000 children and their own neurocognitive outcomes. The latter studies make it possible for the first time to address the second 2020–2025 DGA question.

2. Reviews through 2014

In 2007 the Institute of Medicine of the National Academy of Sciences considered both the nutrients in seafood and results from early seafood studies and concluded that "There is evidence…to suggest that there are benefits to the developing infant, such as improved visual acuity, and improved cognitive development" from eating seafood during pregnancy [5]. The evidence cited by the Institute of Medicine included three prospective cohort studies that found beneficial associations between seafood consumption during pregnancy and visual acuity [8], visual recognition memory [9], and early language and communications skills [10].

In 2009 the Government of Canada issued "Prenatal Nutrition Guidelines for Health Professionals – Fish and Omega-3 Fatty Acids," which recommended that women of childbearing age eat at least five ounces of fish each week based in part on "an association between higher intakes of fish and higher indices of child neurodevelopment" [4]. The Canadian Guidelines cited three prospective cohort studies that reported beneficial associations and also cited the 2007 Institute of Medicine report. The three studies involved visual recognition memory [9], attainment of developmental milestones [11], and improved prosocial behavior, fine motor skills, communication skills, and verbal IQ [12].

In 2010 the scientific advisory committee to the 2010–2015 Dietary Guidelines for Americans (DGAC) concluded that "moderate evidence" indicates at least two servings of seafood per week is associated with improved infant health outcomes including visual acuity and cognitive development [2, p. 239]. Studies cited by the 2010 DGAC included four "methodologically strong" prospective cohort studies that found beneficial associations between seafood consumption during pregnancy and visual recognition memory [9], earlier attainment of developmental milestones [11], improved prosocial behavior, fine motor skills, communication skills, and verbal IQ [12], and improved visual motor ability [13]. Three of the four studies had been cited by the Institute of Medicine or the Government of Canada or both. As an additional matter, the 2010 DGAC excluded results from studies of omega-3 supplements in isolation from its review. It observed that effects attributed to a single nutrient often reflect dietary components acting in synergy. On the basis of the 2010 DGAC's conclusion, the 2010–2015 DGA recommended that pregnant and lactating women eat considerably more seafood than they typically do for "improved infant health outcomes, such as visual and cognitive development" [14, p. 39].

Five years later, the scientific report from the 2015 to 2015 DGAC reiterated the conclusion from 2010 "that moderate evidence supported a positive relationship between maternal dietary intakes of n-3 [omega-3 fatty acids] from seafood and improved cognitive ability in infants" [15, p. 206]. Consequently, the 2015–2020 DGA carried over its recommendation from 2010 that pregnant and lactating women eat more seafood and added that some of that seafood should contain higher amounts of omega-3 fatty acids [16, p. 24].

In 2010 the Food and Agriculture Organization of the United Nations together with the World Health Organization (FAO/WHO) convened an "expert consultation" involving scientists from 11 countries on the risks and benefits of seafood consumption [3]. Their review of the evidence included five prospective cohort studies of seafood consumption cited by the 2010 DGAC, the Government of Canada, and the 2007 report by the Institute of Medicine [9–13]. The expert consultation concluded that "maternal fish consumption lowers the risk of suboptimal neurodevelopment in …offspring compared with the offspring of women not eating fish in most countries evaluated" [3].

In addition to this review, the FAO/WHO expert consultation conducted a quantitative assessment of the net effects on childhood IQ from maternal consumption of nearly 100 species and types seafood. The assessment calculated that all these species and types improve IQ through at least 25 ounces of seafood per week (the assessment's "central estimate"). When the expert consultation deemed mercury in the seafood to be more toxic than calculated in its central estimate, nearly all of the seafood species and types remained beneficial (the assessment's "upper bound estimate") [3].

[1] The Dietary Guidelines for Americans are issued every five years by the U.S. Departments of Agriculture and Health and Human Services. They contain recommendations, nutritional targets and dietary limits for eating a healthy diet. Prior to the issuance of each five-year update, a Dietary Guidelines Advisory Committee issues a scientific report to the Secretaries of Agriculture and Health and Human Services that examines new scientific evidence that may inform revisions to the Dietary Guidelines for Americans.

[2] The 2010-2015 DGA defined seafood as follows: "Seafood is a large category of marine animals that live in the sea and in freshwater lakes and rivers. Seafood includes fish, such as salmon, tuna, trout, and tilapia, and shellfish, such as shrimp, crabs and oysters." We use this definition in this paper. The definition does not include marine mammals.

In 2014, the European Food Safety Authority (EFSA) concluded that "up to 3–4 servings per week during pregnancy has been associated with better functional outcomes of neurodevelopment in children compared to no seafood" [6]. The evidence for this conclusion included nine prospective cohort studies involving whole seafood, six of which had been considered by the Institute of Medicine, the Government of Canada, the 2010 DGAC and the FAO/WHO. The additional three studies were beneficial for motor and spatial functioning [17], verbal IQ and reduced risk of hyperactivity [18], and most subscales on the McCarthy Scales of Children's Abilities [19]. The EFSA also noted that prospective cohort studies involving docosahexaenoic acid (DHA), an omega-3 fatty acid in seafood, had produced inconsistent results and that there was no evidence from DHA supplementation studies during pregnancy for an effect on children's neurodevelopmental outcomes [6, p. 33]. Nonetheless, the EFSA observed that DHA has "an established role in the development of the central nervous system of the foetus" and that seafood is a major provider of DHA during pregnancy as compared to other food sources [6, p. 2].

In 2014 the U.S. Food and Drug Administration (FDA) issued "A Quantitative Assessment of the Net Effects on Fetal Neurodevelopment from Eating Commercial Fish (As Measured by IQ and also by Early Age Verbal Development in Children)" [7]. The FDA assessment included a review of 10 studies that found beneficial associations between seafood consumption during pregnancy and neurocognitive outcomes, seven of which were included in the previously described analyses. The additional three studies indicated seafood consumption benefited IQ and psychomotor development [20], reduced risk of ADHD-related outcomes [21], and increased motor scores [22]. FDA incorporated data into the quantitative assessment from seafood studies that met its inclusion criteria for modeling and cited the others for context. Consistent with the judgement of the DGAC, FDA did not include studies of omega-3 supplementation in its assessment. FDA pointed out that "fish presents a 'package' that includes lean protein, omega-3 fatty acids, selenium, and other minerals and nutrients. In order to capture this 'package,' we modeled results from studies involving fish consumption and did not include results from studies that only measured the contribution from an individual nutrient" [7, p. 72].

The assessment calculated that seafood consumption during pregnancy benefits total and verbal IQ as well as early age verbal development under nearly all consumption circumstances. FDA did not model the net effects of postnatal seafood consumption due to relatively limited data available at that time.

3. The observational nature of the seafood evidence

An advantage of having five times more whole food studies than have been previously considered is that, if methodologically strong, they could lead to a more comprehensive and detailed understanding of the effects of seafood on neurocognition than has previously been possible solely from the empirical data. This is so notwithstanding the fact that all the studies involving maternal seafood consumed during pregnancy have been observational. They have measured associations between seafood consumption and neurocognitive outcomes occurring in study populations without any intervention or controls exercised by the researchers. All of them have been prospective cohort studies that have compared consumption during pregnancy to scores on tests of neurocognition administered to offspring at various ages in childhood. Our search did not identify any randomized controlled trials (RCTs) involving maternal consumption of seafood. Although RCTs are generally considered the most rigorous form of evidence, it is not clear whether such studies are realistically possible for seafood over the course of a pregnancy. Moreover, limitations in RCTs have been increasingly recognized for nutritional research [23]. Given the substantial difficulties in conducting such studies, prospective cohort studies provide a way to evaluate the consequences of eating seafood during pregnancy.

Studies that have examined whether childhood seafood consumption through adolescence affects neurocognition have been a mix of prospective cohort, case-control, and cross-sectional studies, and RCTs. The prospective cohort studies have compared children's seafood consumption at selected ages against test scores at later ages. Cross-sectional studies have compared amounts of seafood to test scores at the same ages. Case-control studies have compared neurocognitive results in children who adhered to diets that included seafood against results in children who did not. Again, amounts of seafood and test scores were measured at the same ages. Measuring children's consumption and their neurocognition at the same age was the most common form of study We found more of them than prospective cohort studies and RCTs combined. They contain greater potential for reverse causality than prospective cohort studies and RCTs, and for that reason cross-sectional studies were not included in the systematic review. We did include the case-control studies but noted the uncertainties. Finally, the RCTs compared test scores in children who were served meals containing seafood in school against scores in children served food containing no seafood, although they could still eat seafood at home.

Our systematic review utilized standards and methodologies of The Nutrition Evaluation Systematic Review (NESR) team within the Center for Nutrition Policy and Promotion in the U.S. Department of Agriculture for evaluating the observational studies and the RCTs. The NESR team conducts systematic reviews of the evidence to assist the analyses of the Dietary Guidelines Advisory Committees. Over the years the DGA has made consumption recommendations on a wide range of subjects based largely on observational evidence after reviewing the strength and quality of that evidence [15, see p. 24].

4. Considerations about benefits

A 2018 policy statement by the American Academy of Pediatrics (AAP) pointed out that "maternal prenatal nutrition and the child's nutrition in the first two years of life (1000 days) are crucial factors in a child's neurodevelopment and lifelong mental health…Failure to provide key nutrients during this critical period of brain development may result in lifelong deficits in brain function despite subsequent nutrient repletion" [24]. The AAP statement cited key nutrients that support neurocognitive development including zinc, iron, choline, folate, iodine, vitamins A, D, B6, and B_{12}, and long-chain polyunsaturated fatty acids (including both omega-3 and omega-6 fatty acids). Seafood is an excellent source of these nutrients[3] and is richer in omega-3s, iodine, vitamin A, vitamin D, and zinc than other common sources of protein[4] [25].

While these nutrients are plausible contributors to neurocognitive development, whether individually, collectively, or synergistically with other nutrients, the most scientific attention over the years has focused on the omega-3 fatty acids in seafood [2,3,5,16], particularly DHA. Seafood is the primary source of DHA in the diet and is generally higher in DHA than all other foods including meats and eggs [5]. The human brain is rich in DHA, particularly in synapses, and the biophysical properties of DHA are needed for optimal synaptic and retinal function [26].

Studies in experimental animals have demonstrated the importance

[3] The possibility that beneficial contributions to the net effects are due to substitution of seafood for less healthy foods is regarded as being unlikely. According to the FAO/WHO, "Based on the observed dose-response relationships and heterogeneity of background diets, it is very unlikely that the benefits of fish are explained to any large extent by the replacement of less "healthy" foods with fish" [3, p. 8].

[4] Seafood is a protein-rich food that, along with other animal sources contain the highest quality proteins. Protein is a source of energy that has been linked to overall growth and development [2] but we are not aware that protein has been linked specifically to neurocognitive development. A nutritional source of benefits to neurocognition must therefore come from the other nutrients.

of brain DHA for optimal neurocognitive development. Omega-3 deficiency during pregnancy and lactation in animal models reduces brain DHA in the offspring and results in lower visual acuity, slower information processing, and abnormal dopaminergic function with behavioral issues that persist into adulthood [27–29]. In humans, omega-3 supplementation during the first 12 months of life has been associated with lasting effects on brain structure, function, and neurochemical concentrations in regions associated with attention and inhibition, nerve health and brain cell signaling [30].

Notwithstanding these findings, we note that RCTs of omega-3 supplementation in isolation during pregnancy and/or lactation have not consistently found benefits to neurocognitive development. A 2016 review by the Agency for Healthcare Research and Quality (AHRQ) [31] as well as the EFSA scientific opinion cited previously [6] and an earlier AHRQ review of omega-3 supplementation studies in 2005 [32] reported that these studies have not shown a consistent effect on offspring neurocognition. It is worth considering whether these null results may have a bearing on the relationship between seafood consumption and neurocognition.

Scientific authorities have not assumed that omega-3s in seafood are the sole source of beneficial effects or act independently of other nutrients. According to the Institute of Medicine, "lack of benefit from EPA/DHA [omega-3 fatty acids in seafood] does not necessarily mean lack of benefit from seafood….other nutrients present in seafood may provide specific health benefits or even facilitate the action of EPA/DHA" [5, p. 70]. Similarly, the FAO/WHO concluded that "the health attributes of fish are most likely due in large part to LCn3PUFAs [omega-3s]. Fish, however, contain other nutrients…that may also contribute to the health benefits of fish" [3, p. 8]. The EFSA also noted the importance of omega-3 fatty acids but took the view that it would be "extreme" to assume that benefits to neurocognition are limited to them [6, p. 38]. As pointed out previously, neither the 2010 DGAC nor the FDA in 2014 considered supplementation studies in their reviews of the evidence relating to seafood consumption and the 2010 DGAC observed that nutrients often act in synergy with other nutrients [2]. It is not clear how studies of omega-3 fatty acids in isolation could capture such effects.

The supplementation RCTs and the seafood studies essentially address different questions. The seafood studies address whether eating seafood under the circumstances of those studies affects neurocognition while the supplementation studies address whether consuming a single nutrient – albeit a potentially important one – in isolation affects neurocognition under the circumstances of those trials. The supplementation circumstances have included an absence of control for seafood consumption, with women eating all the seafood they wanted and in at least one study being encouraged to eat a lot of seafood [33], possibly resulting in some degree of beneficial saturation unrelated to the supplementation. Another circumstance involves the timing of supplementation, which has not begun until the women in trials have become pregnant [29]. Seafood studies more likely reflect habitual diets[5] [34]. Consumption prior to conception may be important for neurocognitive development [35]. Nonetheless, results of the omega-3 supplementation RCTs during pregnancy at least raise the possibility that the beneficial effects seen in the seafood studies are not solely attributable to omega-3 fatty acids.

If seafood does benefit neurocognition, that would raise important questions about how much seafood is beneficial, whether some amounts and types of seafood are more or less beneficial than others (or not beneficial at all), whether the benefits are clinically meaningful, and whether there are optimum amounts of seafood that provide the most possible benefits when eaten over time. As indicated previously, in 2009 the Canadian Government recommended that women of childbearing age eat at least five ounces per week [4]. The 2010 DGAC linked improved cognitive development to "at least two servings of seafood per week [at least eight ounces] during pregnancy" [2, p. 239]. The quantitative net effects modeling performed by the FAO/WHO expert consultation in 2010 calculated IQ gains through at least 28 ounces per week [3] with the greatest gains occurring on average between 16 and 28 ounces. In 2014 the EFSA concluded that "up to 3–4 servings per week" (essentially 12 – 16 ounces) were associated with better functional outcomes of neurodevelopment [6, p. 1] based solely on empirical evidence and not on quantitative modeling as performed by the FAO/WHO or FDA. The EFSA limited its conclusion to 3–4 servings per week because the empirical evidence it reviewed was not informative beyond that amount.

Similar to the FAO/WHO assessment, the FDA 2014 quantitative assessment of net effects calculated gains in IQ that increased to a maximum when an average of 9.1 ounces per week and 12.3 ounces per week were consumed depending on which of two models were used [7]. In one model, the least beneficial fish was still beneficial for IQ up to roughly 40 ounces per week [7, pp. 154–155].

Whether the results from the seafood studies are consistent with all these calculations and estimates or whether the studies indicate a need to revisit or revise them are important questions from a public health standpoint.

5. Considerations about mercury

Interest in the effect of seafood consumption during pregnancy and childhood on neurocognition has included concerns about potential harm from exposure to methylmercury in seafood. Methylmercury is an organic form of mercury that occurs naturally from geologic and biologic processes and accumulates in most if not all seafood in at least trace amounts. It is a neurotoxicant to which the fetal brain and nervous system are particularly sensitive [36].

Early studies that looked for associations between prenatal exposure to mercury and adverse effects on neurocognition in childhood reported mixed results. In the Faroe Islands, for example, where the mercury came mainly from the consumption of pilot whale, researchers reported adverse associations between prenatal exposure to that mercury and neurocognitive outcomes [37]. By contrast, in the Republic of the Seychelles, where exposure to mercury was from marine seafood but not from sea mammals, researchers found no consistent adverse associations with mercury [38]. Prenatal mercury exposure was slightly higher in the Republic of the Seychelles than in the Faroe Islands, but exposure in both populations was roughly ten times higher than that in the United States. In 2000 the National Research Council included whale it its definition of "fish" and recommended that adverse associations on the Boston Naming Test administered in the Faroe Islands serve as the basis for a reference dose for methylmercury [36]. However, in the Republic of the Seychelles there were no adverse associations between mercury and results on the Boston Naming Test at ages nine and 22 years [38,39].

A recent study in the United Kingdom found that children of mothers who had eaten no seafood but had still been exposed to mercury showed a trend toward lower IQ scores while children of mothers who had eaten seafood and had been exposed to the same levels of mercury experienced gains in IQ [40]. Like the Seychelles and Faroe Islands results when compared against each other, this study suggests that the nutrients in seafood can cause seafood to be beneficial notwithstanding the presence of mercury that could otherwise cause a decline in neurocognitive test results. Also, the possibility of significant mercury exposure from other sources, as suggested in the United Kingdom study, including other food sources, was raised in an earlier analysis of data from the United Kingdom [41] and analyses of rice sold in Europe and

[5] A survey conducted by FDA indicated that women who eat seafood during pregnancy already eat seafood. That survey compared consumption of seafood by non-postpartum, non-pregnant women of childbearing age against consumption of seafood by pregnant women. The non-pregnant women typically ate somewhat more seafood than the pregnant women [34].

grown in China [42,43]. In one location in China 34% of the inhabitants exceeded the Environmental Protection Agency's Reference Dose for mercury although seafood only contributed 1–2% of the exposure [43].

Many of the seafood studies in our search measured mercury exposures in addition to amounts of seafood consumed, thus offering the possibility of a better understanding of how high exposures can be before seafood consumption becomes net adverse, regardless of the source of the mercury.

6. Conclusion

The inquiry by the 2020–2025 DGA into the relationships between neurocognition and seafood consumed during pregnancy and consumed by children through adolescence is timely and important. The studies we have identified on the effects on childhood neurocognition from seafood eaten by pregnant women and by children through adolescence have the potential to provide a better understanding about whether and under what circumstances seafood consumption affects neurocognition. Because they are studies of whole food, they inherently reflect the totality of effects from all the constituents in seafood, including nutrients and any toxicants that may be present.

The overwhelming majority of the studies are observational in nature. Randomized controlled trials appear to be impractical to study maternal consumption over an entire pregnancy and may be practical only under limited circumstances for studying children's consumption. Given this background, we have conducted two systematic reviews of studies evaluating seafood as a whole food on neurocognition carefully following the methodologies of the Nutrition Evaluation Systematic Review of the U.S. Department of Agriculture.

Declaration of Competing Interest

The following authors have no conflicts to declare, PS, JRH, GM, JG, MAC, JJS, SLC, JTB, PK-E, BJH, BL, RKM, MFT, SEC. G. Vannice is Director of Nutrition Education and Research for Organic Technologies, an ingredients manufacturer of products that includes omega-3 fatty acids, sterols, tocopherols, and vitamin E concentrates. W.S. Harris is the President of OmegaQuant Analytics, LLC a laboratory that offers fatty acid testing for researchers, clinicians and consumers. N. Salem Jr. is a consultant for DSM Nutritional Products, a company that produces vitamins, carotenoids, nutraceuticals and nutritional lipids including fish oil and various fatty acids.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.plefa.2019.10.001.

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